4. The method of claim 2, wherein said copy number is determined by hybridization to an array of nucleic acid probes.

This amendment is made without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A. For the Examiner's convenience, a complete claim set of the currently pending claims is also submitted herewith as Appendix B.

REMARKS

Change in correspondence address.

Applicants note that a Revocation and Substitute Power of Attorney incorporating a change in correspondence address was filed on April 26, 2001, a copy of which is enclosed. In accordance with the instructions provided on April 26, 2001, **please direct all future correspondence regarding the subject application to CUSTOMER NUMBER 22798, that is:**

22798

PATENT TRADEMARK OFFICE

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Status of the Claims.

Claims 33-70 are pending with entry of this amendment, claims 33-70 being cancelled herein. Claim 4 was amended herein. This amendment introduces no new matter, but merely alters claim dependency to provide proper antecedent basis for the term "copy number". Claims 1-32 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Election/Restriction.

Applicants note with appreciation the rejoining of claims 1-32 as Group I, claims 33-40 as Group II, and claims 51-70 as Group III. Pursuant to a restriction requirement made final, Applicants cancel claims 33-70 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

35 U.S.C. §112, Second Paragraph.

Claims 1-32 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the use of the following terms and phrases:

A) "Copy number" recited in claims 3 and 21;

B) "An increased level of CYP24. . ." in claims 6, 9, and 23;

C) "A statistically significant difference" in claims 15 and 30; and

D) The recitation "a reduced survival expectancy" in claims 18, 23, and 25.

Applicants respectfully traverse.

A) "Copy Number"

The Examiner alleged that claims 3 and 21 were indefinite in the recitation of the term "copy number" because it was allegedly unclear as to what is specifically being measured. The Examiner is reminded that:

> [A] claim is definite if "... read in light of the specification [it] reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits. *Hybritech Inc. v Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81 (Fed. Cir. 1986) cert. denied 480 U.S. 947 (1987).

In the instant case, the term "copy number" is a term of art well known to those of skill. In general the term "copy number" refers to the number of copies of a gene in a cell. Thus, for example, Academic Press Dictionary of Science and Technology (online version) defines "Copy Number" as:

> [T]he number of copies of a specific gene sequence in a genome or entire set of genes present in the haploid cell of a particular organism.

While the Dictionary of Microbiology and Molecular Biology, Second Edition, (John Wiley and Sons, N.Y. 1987) defines "copy number" as:

> The number of copies of *e.g.* a given gene product per copy of that gene (or per cell), **or the number of copies of a given gene per cell**, etc. [emphasis added] (page 227).

In the instant case, claims 2 and 3 recite:

> 2. The method of claim 1, wherein said level of CYP24 is detected by determining **the copy number of CYP24 genes** in the cells of said biological sample.
>
> 3. The method of claim 2, wherein **said copy number is measured using Comparative Genomic Hybridization** (CGH).

Claims 19 and 21 show similar construction. There is no ambiguity whatsoever as to what is specifically being measured. Claim 2 expressly recites that it is the "copy number of CYP24 genes in the cells. . .". That is the number of copies of CYP24 per cell. The phrase is completely unambiguous. It reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and is as precise as the subject matter permits. Accordingly the rejection of claims 3 and 21 under 35 U.S.C. §112, second paragraph, for the use of the term copy number is improper and should be withdrawn.

B) "An increased level of CYP24. . . in claims 6, 9, and 23.

Claims 6, 9, and 23 were rejected under 35 U.S.C. §112, second paragraph, as indefinite because it was allegedly unclear "what amount of RNA or protein is deemed increased". The specification expressly states:

> An "increased level of *CYP24*" **means a level of *CYP24*, that, in comparison with a control level of *CYP24*, is detectably higher**. The method of comparison can be statistical, using quantified values for the level of *CYP24*, or can be compared using non-statistical means, such as by visual assessment by a human. [emphasis added] (page 13, lines 20-23).

The specification is thus completely unambiguous. A detectably higher level of CYP24, *e.g.* in comparison to a control is deemed to be "increased". The phrase reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and is as precise as the subject matter permits. The rejection of claims 6, 9, and 23 under 35 U.S.C. §112, second paragraph, for the use of the term "increased" is therefore improper and should be withdrawn.

C) "A statistically significant difference" in claims 15 and 30.

Claims 15 and 30 were rejected under 35 U.S.C. §112, second paragraph, as indefinite because it was allegedly unclear "how this statistical difference is defined". Applicants respectfully traverse. The specification states:

> **When a quantified level of *CYP24* falls outside of a given confidence interval for a normal level of *CYP24*, the difference between the two levels is said to be "statistically significant."** If a test value falls outside of a given confidence interval for a normal level of *CYP24*, it is possible to calculate the probability that the test value is truly abnormal and does not just represent a normal deviation from the average. In the methods of this invention, a difference between a test sample and a control can be termed "statistically significant" when the probability of the test sample being abnormal can be any of a number of values, including 0.15, 0.1, 0.05, and 0.01. Numerous sources teach how to assess statistical significance, such as Freund, J.E. (1988) Modern elementary statistics, Prentice-Hall.

A "statistically significant difference" is thus expressly defined. Again, the phrase reasonably apprise[s] those skilled in the art both of the utilization and scope of the invention, and is as precise as the subject matter permits. The rejection of claims 15 and 30 under 35 U.S.C. §112, second paragraph, for the use of the phrase "statistically significant difference" is therefore improper and should be withdrawn.

D) "The recitation of "a reduced survival expectancy" in claims 18, 23, and 25.

The Examiner alleged that the recitation ". . . a reduced survival expectancy" in claims 18, 23, and 25 is vague and indefinite. In particular the examiner questioned "how is reduced defined and what sample population is one of skill in the art to compare expectancy levels." In addition, the Examiner alleged that claim 18 is vague and indefinite because the claim does not reveal how the survival expectancy is to be estimated or evaluated.

Applicants respectfully submit that the Examiner has misread claims 18, 23, and 25. **These claims do not require a calculation of expectancy levels or a comparison of expectancy levels.** The language objected to by the Examiner pertains to a conclusion drawn by an observation or measurement of an increased level of CYP24 in the biological sample. In other words, upon observation of an increased level of CYP24, one would conclude that the subject from which the sample is derived would have a reduced survival expectancy as compared to a subject having a normal level of CYP24.

Accordingly claims 18, 23, and 25 are not indefinite and the rejection of these claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled, because the specification while enabling for a method of detecting a predisposition to breast cancer in tissue cultured cell lines, allegedly does not provide a method of detecting a predisposition to

any and all cancers in an animal. In particular the Examiner alleged that the specification does not provide support of the method in any cancer type other than breast cancer. In effect, the Examiner is alleging that applicants haven't shown that the claimed method works for other cancers.

Contrary to the Examiner's assertion, **the claims are not directed to the detection of a predisposition to any and all cancers**. Rather, Applicants assert that where CYP24 levels are elevated, there simply exists a predisposition to cancer. That there may exist cancers that are not associated with elevated CYP24 levels is irrelevant to the validity of the claims.

The Examiner has provided no objective evidence to dispute this assertion. Moreover, Applicants note that the Examiner is implicitly making a utility rejection under 35 U.S.C. §101 alleging that the proposed use of the claimed method lacks credibility. (Under the new guidelines a utility must be specific, substantial, and credible, *see, Official Gazette*, 66(4): 1092-1099). According to the Patent Office's own guidelines:

> Office personnel are reminded that **they must treat as true a statement of fact made by an applicant in relation to an asserted utility**, unless countervailing **evidence** can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. [emphasis added] (*Official Gazette*, 66(4): 1099)

Objective evidence refuting Applicant's claim would require identifying cells in which CYP24 is elevated and there is no increased predisposition to cancer. The Examiner has provided no objective evidence refuting the accuracy of Applicant's claim. Accordingly, the Examiner has failed to make her *prima facie* case under 35 U.S.C. §112, first paragraph, and the rejection on these grounds should be withdrawn.

Prior Art.

Applicants note with appreciation the Examiner's indication that the claims are free of the prior art. In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN 09/285,292 WITH ENTRY OF THIS AMENDMENT

In the specification:

[Not Applicable]

In the claims:

4. The method of claim **[1]2**, wherein said copy number is determined by hybridization to an array of nucleic acid probes.

APPENDIX B

CLAIMS PENDING IN USSN 09/285,292 WITH ENTRY OF THIS AMENDMENT

1. A method of detecting a predisposition to cancer in an animal, said method comprising:

(i) providing a biological sample from said animal;

(ii) detecting the level of CYP24 within said biological sample; and

(iii) comparing said level of CYP24 with a level of CYP24 in a control sample taken from a normal, cancer-free tissue;

wherein an increased level of CYP24 in said biological sample compared to the level of CYP24 in said control sample indicates a predisposition to cancer in said animal.

2. The method of claim 1, wherein said level of CYP24 is detected by determining the copy number of CYP24 genes in the cells of said biological sample.

3. The method of claim 2, wherein said copy number is measured using Comparative Genomic Hybridization (CGH).

4. The method of claim 2, wherein said copy number is determined by hybridization to an array of nucleic acid probes.

5. The method of claim 3, wherein said Comparative Genomic Hybridization is performed on an array.

6 The method of claim 1, wherein said level of CYP24 is detected by measuring the level of CYP24 mRNA in said biological sample, wherein an increased level of CYP24 RNA in said sample compared to CYP24 RNA in said control sample indicates a predisposition to cancer.

7. The method of claim 6, wherein said level of CYP24 mRNA is measured in said biological sample and said control sample at the same vitamin D receptor activity or the CYP24 mRNA levels are normalized to the level of vitamin D receptor activity in the sample and control.

8. The method of claim 6, wherein said level of CYP24 mRNA is measured by hybridization to one or more probes on an array.

9. The method of claim 1, wherein said level of CYP24 is detected by measuring the level of CYP24 protein in said biological sample, wherein an increased level of CYP24 protein in said sample as compared to CYP24 protein in said control sample indicates a predisposition to cancer.

10. The method of claim 9, wherein the level of CYP24 protein is measured in the biological sample and the control sample at the same vitamin D receptor activity or the protein levels are normalized to the level of vitamin D receptor activity in the sample and control.

11. The method of claim 1, wherein said level of CYP24 is detected by measuring the level of 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said biological sample, wherein an increased level of 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said sample as compared to 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said control sample indicates a predisposition to cancer.

12. The method of claim 11, wherein said level of 25-hydroxyvitamin D3 24-hydroxylase activity is measured in said biological sample and said control sample at the same vitamin D receptor activity or the activity levels are normalized to the level of vitamin D receptor activity in the sample and control.

13. The method of claim 1, wherein said animal is a mammal selected from the group consisting of humans, non-human primates, canines, felines, murines, bovines, equines, porcines, and lagomorphs.

14. The method of claim 1, wherein said biological sample is selected from the group consisting of excised tissue, whole blood, serum, plasma, buccal scrape, saliva, cerebrospinal fluid, and urine.

15. The method of claim 1, wherein the difference between said increased level of CYP24 in said biological sample and the level of CYP24 in said control sample is a statistically significant difference.

16. The method of claim 1, wherein said increased level of CYP24 in said biological sample is at least about 2-fold greater than the level of CYP24 in said control sample.

17. The method of claim 1, wherein said increased level of CYP24 in said biological sample is at least about 4-fold greater than said level of CYP24 in said control sample.

18. A method of estimating the survival expectancy of an animal with cancer, said method comprising:

(i) providing a biological sample from said animal;

(ii) detecting the level of CYP24 within said biological sample; and

(iii) comparing said level of CYP24 with the level of CYP24 in a control sample taken from a normal, cancer-free tissue;

wherein an increased level of CYP24 in said biological sample compared to the level of CYP24 in said control sample indicates a reduced survival expectancy in said animal compared to in an animal with cancer that has a normal level of CYP24.

19. The method of claim 18, wherein said level of CYP24 is detected by determining the copy number of CYP24 genes in the cells of said animal.

20. The method of claim 19, wherein said copy number is determined by hybridization to an array of nucleic acid probes.

21. The method of claim 19, wherein said copy number is measured using Comparative Genomic Hybridization.

22. The method of claim 21, wherein said Comparative Genomic Hybridization is performed on an array.

23. The method of claim 18, wherein said level of CYP24 is detected by measuring the level of CYP24 mRNA in said biological sample, wherein an increased level of CYP24 RNA in said sample as compared to CYP24 RNA in said control sample indicates a reduced survival expectancy.

24. The method of claim 23, wherein said level of CYP24 mRNA is measured in said biological sample and said control sample at the same vitamin D receptor activity or the activity levels are normalized to the level of vitamin D receptor activity in the sample and control.

25. The method of claim 18, wherein said level of CYP24 is detected by measuring the level of CYP24 protein in said biological sample, wherein an increased level of CYP24 protein in said sample as compared to CYP24 protein in said control sample, at a given level of vitamin D receptor activity indicates a reduced survival expectancy.

26. The method of claim 18, wherein said level of CYP24 is detected by measuring the level of 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said biological sample, wherein an increased level of 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said sample as compared to 25-hydroxyvitamin D3 24-hydroxylase enzyme activity in said control sample indicates a reduced survival expectancy.

27. The method of claim 26, wherein said level of 25-hydroxyvitamin D3 24-hydroxylase activity is measured in said biological sample and said control sample at the same vitamin D receptor activity or the activity levels are normalized to the level of vitamin D receptor activity in the sample and control.

28. The method of claim 18, wherein said animal is a mammal selected from the group consisting of humans, non-human primates, canines, felines, murines, bovines, equines, porcines, and lagomorphs.

29. The method of claim 18, wherein said biological sample is selected from the group consisting of excised tissue, whole blood, serum, plasma, buccal scrape, saliva, cerebrospinal fluid, and urine.

30. The method of claim 18, wherein the difference between said increased level of CYP24 in said biological sample and the level of CYP24 in said control sample is a statistically significant difference.

31. The method of claim 18, wherein said increased level of CYP24 in said biological sample is at least about 2-fold greater than the level of CYP24 in said control sample.

32. The method of claim 18, wherein said increased level of CYP24 in said biological sample is at least about 4-fold greater than the level of CYP24 in said control sample.